

Claims

1. A taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative, wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups or hydroxyl groups of hyaluronic acid or of hyaluronic acid derivatives, or amino groups of deacetylated hyaluronic acid, optionally by means of a spacer linking the taxane to hyaluronic acid or hyaluronic acid derivative,
with the proviso that the said spacer is different from a hydrazide.
2. The taxane according to claim 1, wherein the taxane is selected from between paclitaxel and docetaxel.
3. The taxane according to claim 1, wherein the said taxane is paclitaxel.
4. The taxane according to claim 1, wherein the hyaluronic acid has a molecular weight of between 400 and 3×10^6 Daltons.
5. The taxane according to claim 4, wherein the hyaluronic acid has a molecular weight of between 400 and 1×10^6 Daltons.
6. The taxane according to claim 4, wherein the hyaluronic acid has a molecular weight of between 400 and 230,000 Daltons.
7. The taxane according to claim 1, wherein the hyaluronic acid is salified with organic and/or inorganic bases.
8. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of esters of hyaluronic acid with alcohols of the aliphatic, araliphatic, cycloaliphatic, aromatic, cyclic and heterocyclic series, said esters having an esterification degree equal to or lower than 50%.
9. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of amides of hyaluronic acid with amines of the aliphatic, araliphatic, cycloaliphatic, aromatic, cyclic and heterocyclic series, said amides having an amidation degree of between 0.1% and 10%.
10. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of O-sulphated derivatives of hyaluronic acid up to the 4th degree of sulphation.

11. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of inner esters of hyaluronic acid having an esterification degree equal to or lower than 15%.
12. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of deacetylates of hyaluronic acid, coming from deacetylation of the N-acetyl-glucosamine unit and having a deacetylation degree of between 0.1% and 30%.
13. The taxane according to claim 1, wherein the hyaluronic acid derivative is selected from the group consisting of percarboxylated derivatives of hyaluronic acid obtained from the oxidation of the primary hydroxyl of the N-acetyl-glucosamine unit, having a percarboxylation degree of between 1 and 100%.
14. The taxane according to claim 1, wherein the covalent bond is formed between hydroxyl groups of the taxane and hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative.
15. The taxane according to claims 1, wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups of hyaluronic acid or of hyaluronic acid derivative.
16. The taxane according to claim 1, wherein the covalent bond is formed between hydroxyl groups of the taxane and amino groups of deacetylated hyaluronic acid.
17. The taxane according to claim 1, wherein the spacer linking the taxane to hyaluronic acid or hyaluronic acid derivative, is selected from the group consisting of aliphatic or araliphatic chains, linear or branched, substituted with one or more groups chosen from hydroxyl, carboxyl, carbonyl, epoxide, acylchloride, thiol, nitril, halogen, anhydride, isocyanate, isothiocyanate and amino groups.
18. The taxane according to claim 17, wherein the spacer is selected from the group consisting of carboxylic acids having from 2 to 18 carbon atoms in the aliphatic or araliphatic chain, substituted with bromine.
19. The taxane according to claim 17, wherein the spacer is selected from the group consisting of carboxylic acids having from 3 to 10 carbon atoms in the aliphatic or araliphatic chain, substituted with bromine.
20. The taxane according to claim 17, wherein the spacer is selected from between 3-bromopropionic acid and 4-bromobutyric acid.

21. The taxane according to claim 1, wherein the covalent bond is an ester bond between the spacer and the hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative.
22. The taxane according to claim 1, wherein the covalent bond is a urethane or thiourethane bond between the spacer and the hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative.
23. The taxane according to claim 1, wherein the covalent bond is an ether bond between the spacer and the hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative.
24. The taxane according to claim 1, wherein the covalent bond is an acetal or ketal bond between the spacer and the hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative.
25. The taxane according to claim 1, wherein the covalent bond is an acetal bond between the hydroxyl groups of hyaluronic acid or of hyaluronic acid derivative and the taxane.
26. The taxane according to claim 1, wherein the covalent bond is an ester bond between the spacer and the carboxyl groups of hyaluronic acid or of hyaluronic acid derivative.
27. The taxane according to claim 1, wherein the covalent bond is an amide bond between the spacer and the carboxyl groups of hyaluronic acid or of hyaluronic acid derivative.
28. The taxane according to claim 1, wherein the covalent bond is an ester bond between the carboxyl groups of hyaluronic acid or of hyaluronic acid derivative and hydroxyl groups of the taxane.
29. The taxane according to claim 1, wherein the covalent bond is an amide bond between the spacer and the amino groups of deacetylated hyaluronic acid.
30. The taxane according to claim 1, wherein the covalent bond is a urethane or thiourethane bond between the spacer and the amino groups of deacetylated hyaluronic acid.
31. The taxane according to claim 1, wherein the covalent bond is a urethane bond between the amino groups of deacetylated hyaluronic acid and hydroxyl groups of the taxane.

32. The taxane according to claim 8, wherein the hyaluronic acid is esterified after the formation of the covalent bond with the taxane.
33. The taxane according to claim 11, wherein the hyaluronic acid is esterified after the formation of the covalent bond with the taxane.
- 5 34. The taxane according to claim 1, wherein the covalent bond is an ester bond between the taxane and the spacer.
35. The taxane according to claim 1, wherein the covalent bond is a urethane or thiourethane bond between the taxane and the spacer.
36. The taxane according to claim 1, wherein the covalent bond is an acetal or
10 ketal bond between the taxane and the spacer.
37. The taxane according to claim 1, wherein the bond percentage between hyaluronic acid and the taxane is between 0.1% and 100%.
38. The taxane according to claim 37, wherein the bond percentage between hyaluronic acid and the taxane is between 0.1% and 35%.
- 15 39. The taxane according to claim 1, wherein the hyaluronic acid or hyaluronic acid derivative enhances the anticancer action of the taxane.
40. The taxane according to claim 11, wherein the inner ester of hyaluronic acid enhances the anticancer action of taxane.
41. The taxane according to claim 26, wherein the hyaluronic acid enhances the
20 anticancer action of taxane.
42. A pharmaceutical composition comprising as the active substance at least a taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41, in combination with pharmaceutically acceptable excipients and diluents.
- 25 43. The pharmaceutical composition according to claim 42, for administration by the oral, intravenous, arterial, intramuscular, subcutaneous, intraperitoneal or transdermal route, or by direct injection into a tumour site.
44. The pharmaceutical composition according to claim 42, for administration by the oral route.
- 30 45. The pharmaceutical composition according to claim 42, wherein the hyaluronic acid or the hyaluronic acid derivative is able to release the taxane into the administration site.

46. The pharmaceutical composition according to any of claims 42-45, further comprising one or more biologically or pharmacologically active substances.
47. The pharmaceutical composition according to claim 46, wherein the said biologically or pharmacologically active substances are selected from the group consisting of steroids, hormones, trophic factors, proteins, vitamins, non-steroid anti-inflammatory drugs, chemotherapy drugs, calcium blockers, antibiotics, antivirals, interleukines and cytokines.
48. The pharmaceutical composition according to claim 46, wherein the said biologically or pharmacologically active substance is interferon.
49. Use of taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41, for the preparation of pharmaceutical compositions useful for the treatment of tumours.
50. Use according to claim 49, wherein the treatment of tumours comprises chemotherapy for breast cancer, cancer of the ovary and/or endometrium, melanoma, lung cancer, cancer of the liver, of the prostate and/or bladder, gastric and/or intestinal cancer, leukaemia and Kaposi's sarcoma.
51. Use of taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41, for the preparation of pharmaceutical compositions useful for the treatment of auto-immune pathologies.
52. Use according to claim 51, wherein the said auto-immune pathologies are selected from the group consisting of rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus, and auto-immune glomerulonephritis.
53. Use of taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41, for the preparation of pharmaceutical compositions useful for the treatment of restenosis.
54. Use of taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41, for the coating of stents and medical devices.
55. Stents and medical devices coated by a taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative as defined in claims 1-41.
56. A process for the preparation of a taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative wherein the covalent bond is an ester bond, said process comprising the following steps:

- A) activating the hydroxyl group of the taxane or, respectively, the carboxyl group of hyaluronic acid or hyaluronic acid derivative by means of an activating agent;
- B) adding the hyaluronic acid or hyaluronic acid derivative or, respectively, the taxane dissolved in a suitable solvent;
- 5 C) optionally purifying the so obtained product.
57. A process for the preparation of a taxane covalently bounded to hyaluronic acid or to a hyaluronic acid derivative wherein the covalent bond is an ester bond, said process comprising the following steps:
- A') preparing the bromide or tosylate of the taxane;
- 10 B') carrying out the nucleophilic substitution of the bromide or tosylate of taxane coming from step A') by the carboxyl group of hyaluronic acid or of hyaluronic acid derivative;
- C') optionally purifying the product obtained.
58. A process for the preparation of a taxane covalently bounded to deacetylated hyaluronic acid wherein the covalent bond is a urethane or thiourethane bond, said
- 15 process comprising the following steps:
- D) activating the hydroxyl group of taxane by means of an activating agent;
- E) adding deacetylated hyaluronic acid dissolved in a suitable solvent;
- F) optionally purifying the so obtained product.
- 20 59. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative wherein the covalent bond is an acetyl bond, said process comprising the following steps:
- G) preparing a solution containing hyaluronic acid or hyaluronic acid derivative and the taxane in a suitable solvent;
- 25 H) adding a simple carbonyl compound such as formaldehyde;
- I) optionally purifying the so obtained product.
60. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least a carboxyl group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid
- 30 derivative by an ester bond, said process comprising the following steps:
- L) activating the carboxyl group of the spacer, possibly previously bounded to the taxane;

M) adding hyaluronic acid or hyaluronic acid derivative;

N) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

5 61. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least a carboxyl group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an ester bond, said process comprising the following steps:

L') substituting the hydroxyl group of hyaluronic acid or hyaluronic acid derivative with a tosyl group or bromide;

10 M'') adding the spacer, possibly previously bounded to the taxane;

N'') optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

15 62. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an anhydride group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an ester bond, said process comprising the following steps:

L'') adding the spacer to a solution containing hyaluronic acid or hyaluronic acid derivative;

M'') optionally purifying the so obtained product;

20 N'') reacting the product coming from step L'') or M'') with the taxane.

63. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an amino group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by a urethane or thiourethane bond, said process comprising the
25 following steps:

O) activating the hydroxyl group of hyaluronic acid or of hyaluronic acid derivative by means of an activating agent;

P) adding the spacer, possibly previously bounded to the taxane;

30 Q) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

64. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an

isocyanate or isothiocyanate group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by a urethane or thiourethane bond, said process comprising the following steps:

O') adding hyaluronic acid or hyaluronic acid derivative to a solution comprising the spacer, possibly previously bounded to the taxane;

P') optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

65. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an epoxy group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an ether bond, said process comprising the following steps:

R) adding the spacer possibly previously bounded to the taxane, to a solution of hyaluronic acid or hyaluronic acid derivative, in the presence of an acid or basic catalyst;

S) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

66. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an hydroxyl group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an ether bond, said process comprising the following steps:

R') substituting the hydroxyl group of hyaluronic acid or hyaluronic acid derivative with a tosyl group or bromide;

S') adding the spacer to the product coming from step R') in a basic environment;

T') optionally purifying the so obtained product;

U') reacting the product coming from step S') or T') with the taxane.

67. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least a carbonyl group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an acetal or ketal bond, said process comprising the following steps:

V) adding the spacer to a solution containing hyaluronic acid or hyaluronic acid derivative in acid or basic environment;

W) optionally purifying the so obtained product;

Z) reacting the product coming from step V) or W) with the taxane.

68. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an hydroxyl group and linking the hydroxyl group hyaluronic acid or the hyaluronic acid derivative by an acetal or ketal bond, said process comprising the following steps:

V') adding a simple carbonyl compound, such as formaldehyde, to a solution containing hyaluronic acid or hyaluronic acid derivative and a spacer possibly previously bounded to the taxane;

W') optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

69. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an hydroxyl group and linking the carboxyl group of hyaluronic acid or the hyaluronic acid derivative by an ester bond, said process comprising the following steps:

a) adding an activating agent to a solution containing hyaluronic acid or hyaluronic acid derivative;

b) adding the spacer possibly previously bound to the taxane, to the solution coming from step a);

c) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

70. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an halogen, such as bromine, and linking the carboxyl group of hyaluronic acid or the hyaluronic acid derivative by an ester bond, said process comprising the following steps:

a') adding the spacer possibly previously bounded to the taxane, to a solution of hyaluronic acid or hyaluronic acid derivative;

b') optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

71. A process for the preparation of a taxane covalently bounded to hyaluronic acid or hyaluronic acid derivative by means of a spacer having at least an amino

group and linking the carboxyl group of hyaluronic acid or the hyaluronic acid derivative by an amide bond, said process comprising the following steps:

d) adding an activating agent to a solution of hyaluronic acid or hyaluronic acid derivative;

5 e) adding the spacer possibly previously bounded to the taxane to the solution coming from step d);

f) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

72. A process for the preparation of a taxane covalently bounded to deacetylated hyaluronic acid by means of a spacer having at least a carboxyl group and linking
10 the amino group of deacetylated hyaluronic acid by an amide bond, said process comprising the following steps:

g) activating with an activating agent the carboxyl group of the spacer possibly previously bounded to the taxane;

15 h) adding a solution containing deacetylated hyaluronic acid;

i) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.

73. A process for the preparation of a taxane covalently bounded to deacetylated hyaluronic acid by means of a spacer having at least an hydroxyl group and linking
20 the amino group of deacetylated hyaluronic acid by a urethane or thiourethane bond, said process comprising the following steps:

l) activating with an activating agent the hydroxyl group of the spacer possibly previously bounded to the taxane;

m) adding the solution containing deacetylated hyaluronic acid;

25 n) optionally purifying the so obtained product, and reacting with the taxane if not previously bounded to the spacer.